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From Myeloma to Plasma Cell Leukemia, Persistent Inequalities

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Abstract

Multiple myeloma (MM) is both a complex and heterogeneous disease. Cytogenetic and molecular abnormalities lead to resistance to treatment and transformation to plasma cell leukemia, which is defined by the presence in circulating blood of plasma cells over 2 G/L, or more than 20% of leukocytes. It is an uncommon hematological malignancy with a poor prognosis. Against this backdrop, we report an observation of multiple myeloma transformed into plasma cell leukemia diagnosed at the Hôpital Principal de Dakar (HPD) that occurred on a 64-year-old man with a history of thyroidectomy followed for multiple myeloma presenting with Salmon et Durie stage IIIA and ISS stage I. Despite a marked improvement in management strategy, myeloma remains an almost invariably incurable disease. However, the development of genetic and molecular biomarkers is necessary to improve its prognosis.

Keywords

Multiple Myeloma, Plasma Cells Leukemia, Personalized Medicine, Risk Stratification

1. Introduction

Multiple myeloma (MM) is a hematological malignancy with plasma cell clonal growth in the bone marrow at more than 10%. It usually occurs with the secretion of complete or incomplete immunoglobulin, and bone lesions that appear at the outset or during the disease [1]. In 2% - 4% of cases, the disease may also progress to plasma cell leukemia (PCL), an aggressive pathology with a dismal prognosis

[2] [3]. Plasma cell leukemia is clinically and genetically distinct from MM [4]. By definition, a blood plasma count greater than 2 G/L, or a plasma cell count greater than 20% of the total white blood cell count, set the diagnosis of PCL. It is considered to be primary form (pPCL) when it occurs de novo in a patient with no reported MM condition, while secondary forms (sPCL) consist of a leukemic transformation of an underlying known MM [5] [6]. Historically, primary PCL is more common than secondary PCL. PCL is uncommon, but its incidence varies from one population to another. In the U.S. SEER (Surveillance, Epidemiology, and End Results) database, between 1973 and 2009, PCL accounted for 0.6% of MM cases, corresponding to around 1200 patients per year in the U.S. [7]. According to the European HAEMACARE project, the crude incidence was 0.4 million, corresponding to 0.5% of all cases of MM [8]. These numbers are lower than previous estimates of 2% - 4% of MM patients [9] [10]. According to the Danish National Registry, between 2005 and 2015, the crude incidence of PCL in Denmark was 1.2 per million, representing around 2% of MM [11]. Due to the rarity of the disease, few studies have been published on large cohorts of PCL patients. No specific biomarker has been identified to predict progression from MM to plasma cell leukemia. In this article, we report an observation of MM transformed into PCL that occurred at the Hôpital Principal de Dakar (Senegal).

2. Observation

A 64-year-old man, with a history of megadolichocolon and thyroidectomy in 2019 under levothyrox, with a notion of intense herbal therapy, followed for multiple myeloma stage IIIA Salmon and Durie and stage I ISS (International Staging System) diagnosed in July 2020, who presented on examination with poorly tolerated anemia, diffuse bone pain and aperformance status (PS) 2. Biological results showed normocytic normochromic anemia at 6.9 g/dL associated with thrombocytopenia at 41 G/L; bone marrow plasmacytosis at 39.3%; corrected serum calcium level at 2.29 mmol/L, serum creatinine level at 13.4 mg/L and a monoclonal electrophoretic peak in the beta zone at 45.6 g/L, characterized by a monoclonal Immunoglobulin A kappa (IgA kappa) band on serum protein immunofixation (IF). Twenty-four-hour proteinuria was 0.25 g/L and urine protein IF showed the presence of kappa light chains. The beta-2-microglobulin (β2m) assay was 3.5 mg/l. No bone signs were observed on radiography. The patient received 12 irregular cycles of Melphalan-Prednisone- Thalidomide chemotherapy, with a partial response at 3 months (61.7%) and a peak reapparition at 6 months of 12.3%. The patient was repeatedly hospitalized, then admitted again in March 2022 with deterioration of general condition PS 4, obnubilation (Glasgow 10/15), and poorly tolerated anemia syndrome. The blood count showed anemia at 3g/dL, thrombocytopenia at 29 G/L, and hyperleukocytosis at 17.9 G/L, with 65% plasma cells in the blood smear (**Figure 1**). Corrected serum calcium was 2.75 mmol/L and the monoclonal peak in the beta zone on serum protein electrophoresis (SPE) was 35.6 g/L (**Figure 2**). The myelogram showed 57% plasma cells (**Figure 3**). The diagnosis of secondary plasma cell leukemia

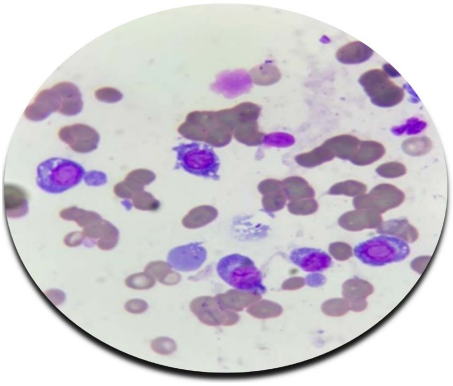
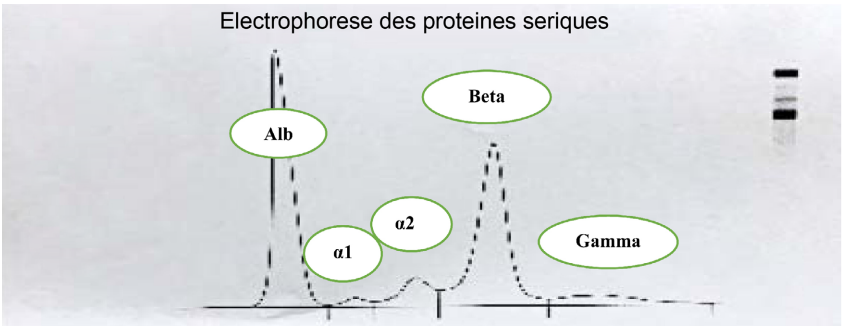


Figure 1. Circulating plasmocytes at relapse on blood smear observed under a light microscope after staining with Ma-Grünwald-Giemsa (MGG), magnification ×100.



Fractions	%	Normes %	Conc.	Normes Conc.
Albumine	41	50.0 - 71.0	34.4	34.0 - 42.0
Alpha 1	1.9	1.4 - 2.9	1.6	1.0 - 3.0
Alpha 2	7.8	7.0 - 11.0	6.6	6.0 - 9.0
Beta	42.4	8.0 - 13.0	35.6	4.0 - 9.0
Gamma	6.9	9.0 - 15.0	5.8	5.0 - 13.0

Commentaire: Pic en zone beta. Immunofixation des proteines seriques a envisager.

Figure 2. Beta zone electrophoretic peak at relapse on serum protein electrophoresis.

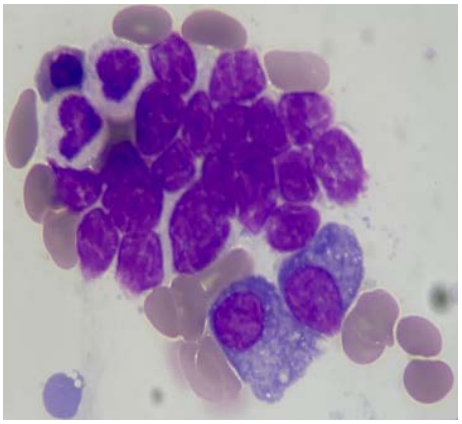


Figure 3. Dystrophic plasma cells on bone marrow smear taken at relapse, observed under light microscope after MGG staining, magnification ×100.

(sPCL) was evoked. Unfortunately, the outcome was fatal, and death occurred after 9 days of hospital stay in the intensive care unit in the context of a shock of probable septic etiology.

3. Discussion

Described over a century ago by Dr. Otto Kahler, it has now been demonstrated that MM is a complex and heterogeneous disease in terms of both genetic and clinical abnormalities [12]. PCL is considered to be the atypical and aggressive form of MM. It is distinguished from MM by its clinical and biological features, its very rapid course, and its poor prognosis. PCL has a classic clinical presentation, associated with asthenia, bone pain, anemia, and hemorrhagic syndrome. However, the clinical course is more aggressive than that of MM, with a greater frequency of extramedullary involvement, essentially liver and spleen involvement, respectively in 52% and 40% of cases of primary PCL and less than 20% of cases of secondary PCL [13]. The frequency of lytic bone lesions is lower (40-60%) than in MM [14]. Our patient's radiograph showed no bone signs. The most frequent laboratory abnormalities are anemia and thrombocytopenia. Anemia is usually severe (Hb < 8.5 g/dL) and most often normocytic normochromic. It is found in 50% of cases [14]. Thrombocytopenia (platelet count below 100 G/L), rare in MM at diagnosis, is present in more than half of PCL patients [5]. In our patient, anemia was 3 g/dl and thrombocytopenia was 29 G/L. PCL plasma cells show immunophenotyping similar to that of MM, with hyperexpression of the surface antigens CD38 and CD138. The adhesion molecule CD56 is most often positive in MM, while the B-cell marker CD20 is also most often positive in PCL [15]. As in MM, translocations involving chromosome 14, t(11;14), t(14;16) and t(4;14) are frequent in PCL [16]. Other deletions are also frequent in PCL, including 1p, 6q, 8p, 13q, 14q, and 16q [17]. MYC rearrangements are also frequently found in PCL [18]. TP53 and DIS3 mutations are more frequent in PCL than in MM, while NRAS, KRAS, and BRAF mutations are less frequently observed in PCL than in MM and LCPs [19]. Other environmental factors may contribute to PCL transformation. The bone marrow microenvironment plays a key role in the pathogenesis of MM by triggering the signaling cascades involved in myeloma cell (MC) proliferation, migration, and survival. Disruption of these mechanisms could be responsible for the development of PCL [12]. Chromosomal instability (CIN) in tumor cells is also affected by the tumor microenvironment [20]. It has been observed that the bone marrow (BM) microenvironment in MM is more hypoxic than that of a normal BM, and that hypoxia is associated with dissemination of CMs [21]. Hypoxia in the bone marrow microenvironment is associated with increased DNA impairments [22]. In addition, the poorly oxygenated niche and hypoxia-induced glycolytic metabolism have been associated with chemotherapy resistance in MM patients [23] [24]. Chromothripsis and chromoplexis are forms of CIN that lead to structural alterations. Chromothripsis, which involves a maximum of two chromosomes, is associated with lagging chromosomes due to chromosome mis-segregation [25]. Some chromo-

somes are more affected than others: chromosomes 1 (5.1%), 14 (2.4%) and 11 (2.3%) [26]. Chromothripsis is the only independent structural variant associated with unfavorable progression-free survival (PFS) overall survival (OS), and a high mutational load. This form of structural CIN could explain why some patients relapse rapidly and have poorer survival [27]. Chromoplexia results in complex DNA rearrangements, usually affecting three or more chromosomes [28]. Interestingly, chromosomes 8, 14, and 11 were the most frequently affected. Genomic instability may contribute to many features of MM, such as its genetic complexity, therapeutic resistance, and frequent relapses [29]. Numerous mutations in genes encoding adhesion molecules (CD56, N-CAM, I-CAM, LFA...) have been shown to cause a loss of affinity of PCL plasma cells for the bone marrow stroma, leading to their extramedullary passage [30] [31]. Cytokines are also involved in PCL, in particular interleukin-6 (IL-6). Increased CD27 expression has been reported to play a role in activating anti-apoptotic pathways and nuclear factor-kB, which plays a crucial role in the survival of malignant plasma cells. This may have therapeutic implications, given that this pathway can be inhibited by proteasome inhibitors (bortezomib, carfilzomib...) [12]. In our case, no cytogenetic or molecular biology analysis was carried out due to financial and technical barriers. As a result, treatment cannot be adapted according to risk stratification. This case study shows the importance of cytogenetic and molecular analysis in the diagnosis of the disease to better anticipate the evolution of the pathology. Detection of rearrangements such as t(4;14), t(14;16), del(13q14), or del(17p13) would have enabled the introduction of complementary therapies [32]. PCL remains a very rare entity that has not been sufficiently studied due to the absence of a sufficiently large cohort. There is therefore no gold-standard treatment for PCL, particularly secondary PCL, which is considered and treated as relapsed/refractory MM [32]. Studies show that thanks to therapeutic advances in recent years (immunomodulators, stem cell transplants, monoclonal antibodies, etc.), the median overall survival (OS) of patients with pPLC has improved from 5 months to around 24 months. Nevertheless, a recent analysis taking cytogenetic status into account nuances these results, showing that a patient with pPLC considered to be at high cytogenetic risk had an average overall survival of 19 months. As for pPLC, overall survival remains appalling, with a median of 4.2 months [33]. However, given the rarity and relatively short course of PCL, much remains to be discovered for both primary and secondary forms of the disease [32]. Patients with much lower levels of circulating plasma cells (≥ 5%) have been shown to have similar poor outcomes [34] [35]. Further studies will be essential to better stratify cytogenetic and molecular risks and their clinical repercussions, and thus to develop more appropriate treatment regimens.

4. Conclusion

Despite a notorious improvement in treatment strategy in recent years, with several major innovations in terms of both molecule development and therapeutic sequences, myeloma remains an almost invariably incurable disease. Biologi-

cal and cytogenetic impairments imply resistance to treatment, and blood and extra-bony invasion of plasmacytosis, giving this form a dismal prognosis. PCL shares common features with MM, but also presents clinical, biological, and prognostic particularities. However, the development of genetic and molecular biomarkers is needed to propose effective therapy and improve prognosis.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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